PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classificati n 6 :
A61K 7/48

A1

(11) International Publicati n Number: WO 98/00102

(43) International Publication Date: 8 January 1998 (08.01.98)

(21) International Applicati n Number: PCT/EP97/01625

(22) International Filing Date: 29 March 1997 (29.03.97)

(30) Priority Data:
60/022,509 28 June 1996 (28.06.96) US

(71) Applicant *(for AU BB CA GB IE IL KE LC LK LS MN MW NZ SD SG SZ TT UG only)*: UNILEVER PLC [GB/GB]; Unilever House, Blackfriars, London EC4P 4BQ (GB).

(71) Applicant *(for all designated States except AU BB CA GB IE IL KE LC LK LS MN MW NZ SD SG SZ TT UG)*: UNILEVER N.V. [NL/NL]; Weena 455, NL-3013 AL Rotterdam (NL).

(72) Inventors: ZNAIDEN, Alexander, Paul; 110 Fox Road, Trumbull, CT 06611 (US). CROTTY, Brian, Andrew; 46 Damascus Road, Branford, CT 06405 (US). JOHNSON, Anthony, William; 211 Papermill Lane, Fairfield, CT 06430 (US).

(74) Agent: ROTS, M., J., F.; Unilever plc, Patent Division, Colworth House, Sharnbrook, Bedford MK44 1LQ (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: VITAMIN C DELIVERY SYSTEM

(57) Abstract

A cosmetic composition is provided which includes ascorbic acid (Vitamin C) stabilized by dimethyl isosorbide in a pharmaceutically acceptable carrier. Among the preferred carriers are polyols such as polyethylene glycol, propylene glycol and mixtures thereof. Aesthetic properties are improved by the presence of a cross-linked non-emulsifying siloxane elastomer and a volatile siloxane.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

VITAMIN C DELIVERY SYSTEM

BACKGROUND OF THE INVENTION

Field of the Invention

The invention relates to a cosmetic product that can stably store ascorbic acid and then deliver same to the skin.

The Related Art

Ascorbic acid, also known by its common name of Vitamin C, has long been recognized as an active substance benefiting skin appearance. Vitamin C reportedly increases the production of collagen in human skin tissue. Wrinkles and fine lines are thereby reduced. An overall healthier and younger-looking appearance results. Vitamin C has also found utility as an ultraviolet ray blocking or absorbing agent. Whitening or bleaching skin compositions have also employed Vitamin C utilizing its property of interference with the melanin formation process. There also is a belief that ascorbic acid interacts with the human immune system to reduce sensitivity to skin aggravating chemicals. Reduced levels of Vitamin C concentration on the skin have also been implicated with an increase in stress. From all of the foregoing perspectives, Vitamin C or ascorbic acid may provide significant benefit when topically applied.

Unfortunately, Vitamin C is a very unstable substance. Although it is readily soluble in water, rapid oxidation occurs in aqueous media. Solubility of ascorbic acid has been reported to be relatively poor in nonaqueous media,

thereby preventing an anhydrous system from achieving any significant level of active concentration.

The art has sought to overcome the problem in a variety of ways. One approach is the preparation of ascorbic acid derivatives. These derivatives have greater stability than the parent compound and, through biotransformation or chemical hydrolysis, can at the point of use be converted to the parent acid. For instance, U.S. Patent 5,137,723 (Yamamoto et al) and U.S. Patent 5,078,989 (Ando et al) provide glycosylate and ester derivatives, respectively.

U.S. Patent 4,818,521 (Tamabuchi) describes under the background technology a so-called two-pack type cosmetic wherein Vitamin C powder and other ingredients are separately packaged in different containers with mixing just prior to use of the cosmetic. The mixing procedure and expensive packaging were said to be drawbacks of this system. The patent suggests stable oil-in-water type emulsions that are weakly acidic and wherein ascorbic acid has been premixed with a stabilizing oil.

Maintenance of pH below about 3.5 has also been suggested in U.S. Patent 5,140,043 (Darr et al) as a stabilization means for aqueous compositions of ascorbic acid.

Water compatible alcohols such as propylene glycol, polypropylene glycol and glycerol have been suggested as co-carriers alongside water to improve stability. An illustration of this approach can be found in U.S. Patent 4,983,382 (Wilmott and Znaiden). Therein a blend of water and water-miscible organic solvent are combined as a stabilizing system. At least about 40% of the organic solvent must be ethanol while the remainder may be selected from such alcohols as propylene glycol, glycerin, dipropylene glycol and polypropylene glycol.

Japanese Patent 44-22312 (Shionogi) describes the stabilization of Vitamin C in a mainly aqueous medium by a variety of glycols. These include polyethylene glycol, ethylene glycol, diethylene glycol and even ethanol. These formulations are intended for ingestion.

U.S. Patent 4,372,874 (Modrovich) has reported incorporation of relatively large amounts of ascorbic acid in a polar water-miscible organic solvent such as dimethyl sulfoxide. Levels of water are kept below 0.5% through addition of a particulate desiccant to the carrier. Although highly polar systems such as dimethyl sulfoxide may be effective, this and related carriers are toxicologically questionable.

Accordingly, it is an object of the present invention to provide a delivery system for ascorbic acid in which the compound is storage stable.

Another object of the present invention is to provide a delivery system which assists the penetration of ascorbic acid into the human skin while avoiding irritation thereof.

Still another object of the present invention is to provide a system for delivering ascorbic acid that is aesthetically pleasing and imparts a soft and smooth skinfeel.

These and other objects of the present invention will become more readily apparent through the following summary, detailed discussion and Examples.

SUMMARY OF THE INVENTION

A cosmetic composition is provided that includes:

(i) from 0.001 to 50% by weight of ascorbic acid;

(ii) from 0.5 to 20% by weight of dimethyl isosorbide; and

(iii) a pharmaceutically acceptable carrier present in an effective amount to deliver the ascorbic acid to skin.

A method is also provided for stabilizing ascorbic acid involving adding dimethyl isosorbide in a stabilizing amount to the ascorbic acid in the presence of a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION OF THE INVENTION

Now it has been discovered that ascorbic acid can be stabilized against decomposition through use of dimethyl isosorbide in a pharmaceutically acceptable carrier. Dimethyl isosorbide is known in *Chemical Abstracts* as 1,4:3,6 dianhydro-2,5-di-*o*-methyl-D-glucitol. Commercially it is available from ICI Surfactants under the trademark Arlasolve DMI. Amounts of this material may range from 0.5 to 20%, preferably from 1 to 10%, optimally from 1.5 to 8% by weight.

Ascorbic acid is available from several sources including Roche Chemicals. Amounts of this material may range from 0.001 to 50%, preferably from 0.1 to 10%, optimally from 1 to 10% by weight.

Compositions of this invention will require a pharmaceutically acceptable carrier. Generally the carrier will be an ingredient present in highest amounts in the cosmetic composition. These amounts may range from 10 to 99.9%, preferably from 25 to 90%, optimally from 50 to 85% by weight. Pharmaceutically acceptable carriers may be

selected from water, polyols, silicone fluids, esters and mixtures thereof. When present, water may range from 0.5 to 20%, preferably from 1 to 10%, usually from 2 to 6%, optimally less than 5% by weight of the composition.

Advantageously one or more polyols are present as carriers in the compositions of this invention. Illustrative are propylene glycol, dipropylene glycol, polypropylene glycol, polyethylene glycol, sorbitol, hydroxypropyl sorbitol, hexylene glycol, 1,3-butylene glycol, 1,2,6-hexanetriol, glycerin, ethoxylated glycerin, propoxylated glycerin and mixtures thereof. Most preferably the polyol is a mixture of polyethylene glycol, molecular weight ranging from 200 to 2,000, and propylene glycol. Preferred weight ratios of polyethylene glycol to propylene glycol range from 5:1 to 1:10, preferably from 2:1 to 1:5, more preferably from 2:1 to 1:2, optimally 1:1 to 1:2. Amounts of the polyol may range from 1 to 50%, preferably from 10 to 40%, optimally from 25 to 35% by weight of the composition.

Silicone oils may also be included as carriers in the compositions of this invention. These oils may be either volatile or nonvolatile. The term "volatile" as used herein refers to those materials which have a measurable vapour pressure at ambient temperature. Volatile silicone oils are preferably chosen from cyclic or linear polydimethylsiloxanes containing from about 3 to about 9, preferably from about 4 to about 5, silicon atoms. Cyclomethicone is the common name of the preferred volatile silicone oil and is available as a tetramer or pentamer. Amounts of the volatile siloxane will range from 10 to 80%, preferably from 20 to 70%, optimally from 30 to 65% by weight of the composition.

Linear volatile silicone materials generally have viscosities less than about 5 centistokes at 25°C while

cyclic materials typically have viscosities of less than about 10 centistokes.

Examples of preferred volatile silicone oils useful herein include: Dow Corning 344, Dow Corning 345 and Dow Corning 200 (manufactured by Dow Corning Corp.); Silicone 7207 and Silicone 7158 (manufactured by the Union Carbide Corp.); SF 1202 (manufactured by General Electric); and SWS-03314 (manufactured by SWS Silicones, Inc.).

The nonvolatile silicone oils useful in compositions of this invention are exemplified by the polyalkyl siloxanes, polyalklyaryl siloxanes and polyether siloxane copolymers. The essentially nonvolatile polyalkyl siloxanes useful herein include, for example, polydimethyl siloxanes with viscosities of from about 5 to about 100,000 centistokes at 25°C. Among the preferred nonvolatile silicones useful in the present compositions are the polydimethyl siloxanes having viscosities from about 10 to about 400 centistokes at 25°C. Such polyalkyl siloxanes include the Viscasil series (sold by General Electric Company) and the Dow Corning 200 series (sold by Dow Corning Corporation). Polyalkylaryl siloxanes include poly(methylphenyl)siloxanes having viscosities of from about 15 to about 65 centistokes at 25°C. These are available, for example, as SF 1075 methylphenyl fluid (sold by General Electric Company) and 556 Cosmetic Grade Fluid (sold by Dow Corning Corporation). Useful polyether siloxane copolymers include, for example, a polyoxyalkylene ether copolymer having a viscosity of about 1200 to 1500 centistokes at 25°C. Such a fluid is available as SF-1066 organosilicone surfactant (sold by General Electric Company). Cetyl dimethicone copolyol and cetyl dimethicone are especially preferred because these materials also function as emulsifiers and emollients. The former material is available from Goldschmidt AG under the trademark Abil EM-90. Amounts of the nonvolatile siloxane

may range from 0.1 to 40%, preferably from 0.5 to 25% by weight of the composition.

Esters may also be incorporated into the cosmetic compositions as pharmaceutically acceptable carriers. Amounts may range from 0.1 to 50% by weight of the composition. Among the esters are:

(1) Alkyl esters of fatty acids having 10 to 20 carbon atoms. Methyl, isopropyl, and butyl esters of fatty acids are useful herein. Examples include hexyl laurate, isohexyl laurate, isohexyl palmitate, isopropyl palmitate, decyl oleate, isodecyl oleate, hexadecyl stearate, decyl stearate, isopropyl isostearate, diisopropyl adipate, diisohexyl adipate, dihexyldecyl adipate, diisopropyl sebacate, lauryl lactate, myristyl lactate, and cetyl lactate. Particularly preferred are C_{12}-C_{15} alcohol benzoate esters.

(2) Alkenyl esters of fatty acids having 10 to 20 carbon atoms. Examples thereof include oleyl myristate, oleyl stearate, and oleyl oleate.

(3) Ether-esters such as fatty acid esters of ethoxylated fatty alcohols.

(4) Polyhydric alcohol esters. Ethylene glycol mono and di-fatty acid esters, diethylene glycol mono- and di-fatty acid esters, polyethylene glycol (200-6000) mono- and di-fatty acid esters, propylene glycol mono- and di-fatty acid esters, polypropylene glycol 2000 monooleate, polypropylene glycol 2000 monostearate, ethoxylated propylene glycol monostearate, glyceryl mono- and di-fatty acid esters, polyglycerol poly-fatty esters, ethoxylated glyceryl monostearate,

1,3-butylene glycol monostearate, 1,3-butylene glycol distearate, polyoxyethylene polyol fatty acid ester, sorbitan fatty acid esters, and polyoxyethylene sorbitan fatty acid esters are satisfactory polyhydric alcohol esters.

(5) Wax esters such as beeswax, spermaceti, myristyl myristate, stearyl stearate.

(6) Sterols esters, of which cholesterol fatty acid esters are examples thereof.

Aesthetic properties and stabilization of emulsions incorporating the Vitamin C may be improved through addition of a crosslinked non-emulsifying siloxane elastomer. Average number molecular weight of these elastomers should be in excess of 10,000, preferably in excess of 1 million and optimally will range from 10,000 to 20 million. The term "non-emulsifying" defines a siloxane from which polyoxyalkylene units are absent. Preferably the crosslinked non-emulsifying siloxane elastomer is formed from a divinyl monomer reacting with Si-H linkages of a siloxane backbone. Illustrative of the elastomer is a material with the CTFA name of Crosslinked Stearyl Methyl-Dimethyl Siloxane Copolymer, available as Gransil SR-CYC (25-35% active elastomer) from Grant Industries, Inc., Elmwood Park, New Jersey. Supply of related elastomer may also be available from the General Electric Company.

Amounts of the elastomer may range from 0.1 to 30%, optimally from 1 to 25%, most preferably from 10 to 20% by weight of the composition.

Minor adjunct ingredients may also be included in cosmetic compositions of this invention. These ingredients may be selected from preservatives, fragrances, anti-foam agents,

opacifiers, colorants and mixtures thereof, each in their effective amounts to accomplish their respective functions.

The following examples will more fully illustrate the embodiments of this invention. All parts, percentages and proportions referred to herein and in the appended claims are by weight unless otherwise indicated.

EXAMPLE 1

Stabilization of ascorbic acid by dimethyl isosorbide was evaluated in the experimental and control formulations outlined under Table I. These formulations were placed in a temperature control oven at 110°F. The amount of remaining ascorbic acid was then measured at intervals of 2, 4 and 8 weeks.

TABLE I

Test Formulations

COMPONENT	Example No. (Weight %)	
	1	1A (CONTROL)
Cyclomethicone	42.0	42.0
Gransil SR CYL	18.0	18.0
Polyethylene Glycol 200	20.3	21.0
Dimethyl Isosorbide	10.0	--
Ascorbic Acid	5.0	5.0
Cetyl Dimethicone Copolyol	0.8	0.8
Water	balance	balance

Essentially no degradation of ascorbic acid occurred in the presence of dimethyl isosorbide. By contrast, the control formulation lost approximately 10% ascorbic acid over the eight week period. The data is shown in Table II.

TABLE II

Ascorbic Acid Storage Stability at 110°F

COMPONENT	Example No. (% Ascorbic Acid Remaining)	
	1	1A (CONTROL)
Initial	100	100
2 Weeks	99	83
4 Weeks	99	93
8 Weeks	99	91

EXAMPLES 2-5

A series of further examples were prepared. Their compositions are outlined under Table III. These formulations provided good storage stability for the ascorbic acid and were judged to be aesthetically consumer acceptable.

TABLE III

COMPONENT	Example No. (Weight %)			
	2	3	4	5
Cyclomethicone	42.0	41.6	40.0	42.0
Gransil SR CYL	18.0	17.9	17.3	18.0
Propylene Glycol	16.8	14.8	17.5	15.0
Polyethylene Glycol 200	11.0	13.7	13.5	13.5
Ascorbic Acid	5.0	5.0	5.0	5.0
Dimethyl Isosorbide	2.0	2.0	2.0	2.0
Cetyl Dimethicone Copolyol	0.8	0.8	0.8	0.8
Water	balance	balance	balance	balance

EXAMPLES 6-12

These series of Examples illustrate the scope of the present invention. Various concentrations and different glycol carriers are illustrated.

TABLE IV

COMPONENT	Example No. (Weight %)						
	6	7	8	9	10	11	12
Cyclomethicone	36.0	36.0	36.0	40.0	40.0	45.0	32.0
Gransil SR CYL	24.0	24.0	24.0	20.0	20.0	15.0	27.0
Butylene Glycol	17.5	--	17.5	--	--	--	29.0
Glycerin	--	17.5	--	--	--	--	--
Polyethylene Glycol 200	10.0	--	--	17.5	12.0	10.0	10.0
Polyethylene Glycol 800	--	10.0	10.0	10.0	12.0	10.0	--
Dimethyl Isosorbide	2.0	2.0	2.0	4.0	8.0	10.0	1.0
Ascorbic Acid	1.0	1.0	1.0	4.0	4.0	8.0	0.5
Cetyl Dimethicone Copolyol	0.8	0.8	0.8	0.8	0.8	--	--
Water	bal.	bal.	bal.	bal.	bal.	bal.	bal.

The foregoing description and Examples illustrate selected embodiments of the present invention and in light thereof variations and modifications will be suggested to one skilled in the art, all of which are within the spirit and purview of this invention.

CLAIMS

1. A cosmetic composition comprising:

(i) from 0.001 to 50% by weight of ascorbic acid;

(ii) from 0.5 to 20% by weight of dimethyl isosorbide; and

(iii) a pharmaceutically acceptable carrier present in an effective amount to deliver the ascorbic acid to skin.

2. The composition according to claim 1 wherein the carrier comprises a polyol in an amount from 1 to 50% by weight of the composition.

3. The composition according to claim 2 wherein the polyol is selected from the group consisting of propylene glycol, dipropylene glycol, polypropylene glycol, polyethylene glycol, sorbitol, hydroxypropyl sorbitol, hexylene glycol, 1,3-butylene glycol, 1,2,6-hexanetriol, glycerin, ethoxylated glycerin, propoxylated glycerin and mixtures thereof.

4. The composition according to claim 2 wherein the polyol is a mixture of polyethylene glycol and propylene glycol in a weight ratio of 2:1 to 1:2.

5. The composition according to any one of claims 1-4 wherein the carrier comprises water in an amount less than 5% by weight of the composition.

6. The composition according to any one of claims 1-5 wherein the amount of ascorbic acid ranges from 0.1 to 10% by weight of the composition.

7. The composition according to any one of claims 1-6 further comprising from 0.1 to 30% of a crosslinked non-emulsifying siloxane elastomer.

8. The composition according to claim 7 wherein the crosslinked non-emulsifying siloxane elastomer is formed from a divinyl monomer reacting with Si-H linkages of a siloxane backbone.

9. The composition according to any one of claims 1-8 further comprising from 10 to 80% of a volatile siloxane.

INTERNATIONAL SEARCH REPORT

Int. ...nal Application No
PCT/EP 97/01625

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 983 382 A (WILMOTT JAMES M ET AL) 8 January 1991 cited in the application see the whole document ---	1-4,6
Y	US 4 923 900 A (DE VILLEZ RICHARD L) 8 May 1990 see column 1, line 60-68 see column 2, line 1-8 see column 3, line 48-68 see column 4, line 54-59 see claims 1,2,8,10,14,18 ---	1-4,6
Y	US 4 818 521 A (TAMABUCHI HIROSHI) 4 April 1989 cited in the application see the whole document --- -/--	1-6

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 July 1997	04.08.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Sierra Gonzalez, M

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 228 162 A (LUZZI LOUIS A ET AL) 14 October 1980 see column 1, line 46-68 see column 2, line 1-15 see column 2, line 66-68 see column 3, line 1-25 see claims 1-4	1-6
A	WO 90 12752 A (EBCO MFG CO) 1 November 1990 cited in the application see the whole document	1-9
A	CHEMICAL ABSTRACTS, vol. 105, no. 20, 17 November 1986 Columbus, Ohio, US; abstract no. 178434, A. TUOMI: "Stabilized injection of indomethacin" XP002035260 see abstract & FI 69 565 B (OSAKEYHTIO STAR AB) 29 November 1985	1-9

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4983382 A	08-01-91	CA 1325774 A	04-01-94
		JP 1254609 A	11-10-89
US 4923900 A	08-05-90	US 5086075 A	04-02-92
US 4818521 A	04-04-89	NONE	
US 4228162 A	14-10-80	CA 1142091 A	01-03-83
		EP 0023772 A	11-02-81
		JP 1014205 B	10-03-89
		JP 1530704 C	15-11-89
		JP 56032425 A	01-04-81
WO 9012752 A	01-11-90	AU 5644190 A	16-11-90
		CA 2031533 A	26-10-90
		EP 0426811 A	15-05-91